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International application number: PCT/EP04/014077

International filing date: 10 December 2004 (10.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: EP  
Number: 03028441.8  
Filing date: 11 December 2003 (11.12.2003)

Date of receipt at the International Bureau: 17 February 2005 (17.02.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland  
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**Patentanmeldung Nr.    Patent application No.    Demande de brevet n°**

03028441.8

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des brevets

PCT/EP2004/014077

10.12.04

Anmeldung Nr:  
Application no.: 03028441.8  
Demande no:

Anmeldetag:  
Date of filing: 11.12.03  
Date de dépôt:

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.  
If no title is shown please refer to the description.  
Si aucun titre n'est indiqué se référer à la description.)

Hydroxylamine derivatives

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)  
revendiquée(s)  
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/  
Classification internationale des brevets:

C07C/

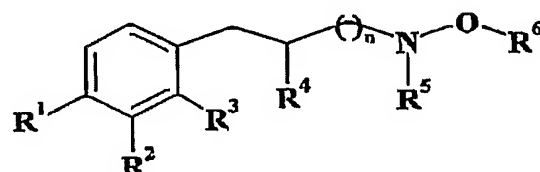
Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of  
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL  
PT RO SE SI SK TR LI



## HYDROXYLAMINE DERIVATIVES

This invention is related to hydroxylamino derivatives of the following general formula (I)



(I)

wherein

- 5        n is 0, 1 or 2;  
      R<sup>1</sup> and R<sup>2</sup>, independently of each other, are H, OH or OCH<sub>3</sub>;  
      R<sup>3</sup> is H or CH<sub>3</sub>;  
      R<sup>4</sup> is H, C<sub>1</sub>-C<sub>3</sub> straight or branched alkyl or, together with R<sup>3</sup>, forms a  
      five to seven-membered carbocyclic ring;  
10       and R<sup>5</sup> and R<sup>6</sup>, independently of each other, are H or C<sub>1</sub>-C<sub>5</sub> straight or  
      branched alkyl

and the pharmaceutically acceptable salts or prodrug thereof, for the  
preparation of medicaments useful for the prevention, treatment and diagnosis  
of CNS degenerative disorders related to protein misfolding and/or  
15       misaggregation.

The invention also relates to novel compounds included in the above  
formula (I), to a method for preparing said compounds and to pharmaceutical  
compositions containing them.

### FIELD OF INVENTION

20       The present invention relates to novel compounds, pharmaceutical  
compositions containing said compounds and their use in the treatment and  
diagnosis of CNS degenerative disorders such as those caused by formation of

fibrils of beta-amyloid peptide, alpha-synuclein, prion protein and huntingtin, Alzheimer's Disease, systemic AA amyloidosis, Lewy body disease, Parkinson's Disease, spongiform encephalopathies and Huntington's Disease.

## BACKGROUND OF THE INVENTION

5 In recent years it has been found that several neurodegenerative disorders are caused by protein misfolding and/or misaggregation.

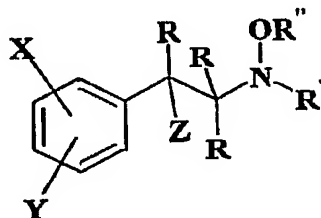
One of the most important and initial step of Alzheimer's disease (AD), for instance, involves proteolytic cleavage of APP (amyloid precursor protein,) releasing short 40, 42 and 43 aa peptides (beta amyloid 1-40, 1-42,  
10 and 1-43). The degeneration of neurons is due to polymerization of beta-amyloid peptides ( $A\beta$ ) and subsequent neuronal deposit (amyloid). Monomeric  $A\beta$  is a product of normal metabolism and is not toxic to neuronal cells. As it forms multimeric and polymeric assemblies of itself,  $A\beta$  acquires potent toxicity for neuronal cells. Inhibition of this polymerization process has thus  
15 been identified as a potential approach to the treatment of AD and all other related pathologies where the anatomopathological hallmark is the presence of  $A\beta$  deposit.

Amyloid like-disorders might be far more widespread than previously thought, and might include many common neurodegenerative and  
20 neuromuscular pathologies, as well as prion disease. Prion diseases can be either sporadic or infectious, and until recently were not known to be associated with protein misfolding and deposition. Prions are composed solely of a misfolded prion protein ( $PrP^{Sc}$ ) isoform of a glycolipid-anchored host protein. Patients with prion diseases develop progressive neurologic  
25 dysfunction. Prion diseases are invariably fatal and no effective therapy exists till now. Compounds that inhibit  $PrP^{Sc}$  formation including Congo red, are effective in scrapie-infected cultured cells.

It has also been found that the formation of intraneuronal deposits

called Lewy bodies and Lewy neurites is due to aggregates of another protein, alpha-synuclein, whose misfolding and misaggregation is also believed to be one of the causes of both AD and Parkinson's disease.

US 3,184,510 discloses N-alkoxy and N-hydroxyphenylethylamines of  
5 the following general formula:



wherein

X and Y, independently of each other, are H, OH or OCH<sub>3</sub>;

Z is H or OH;

R is H or CH<sub>3</sub>;

10 R' is H, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub> or *i*-C<sub>3</sub>H<sub>7</sub>;

R'' is CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub> or *i*-C<sub>3</sub>H<sub>7</sub>

and their use for sustaining and/or raising blood pressure, their use as local vasoconstrictors and/or in the relaxation of the bronchial smooth muscles and of the intestinal tract, in pupil dilation and in the  
15 stimulation of adrenergic nerves. No CNS activity was disclosed.

GB 1,062,299 discloses 3,4-dihydroxyphenyl-propane derivatives of the general formula Ar-CH<sub>2</sub>-C(CH<sub>3</sub>)-NH(OR), wherein Ar is 3,4-dihydroxyphenyl and R is H or C<sub>1</sub>-C<sub>8</sub> alkyl, as hypertensive agents.

Major, R. T. and Ohly, K. W. J. (Med. and Pharmaceut. Chem. 1961, 4,  
20 51-65) described the synthesis of N-alkoxy-N-(2-phenyl)-isopropylamines of formula C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)NHOR wherein R is CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub> or *i*-C<sub>3</sub>H<sub>7</sub>, and tested the compounds for MAO inhibitory activity.

Benington, F.; Morin, R. D. and Clark, L. C. Jr. (J. Med. Chem. 1965,

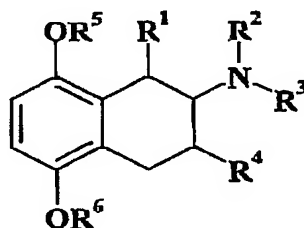


8, 100-104) described the synthesis of ring-substituted 1-aryl-2-hydroxyamino- and 1-aryl-2-methoxyamino-propanes and demonstrated that the compounds were general central stimulants.

Kende *et al.* described in Tetrahedron Letters 1991, 14, 1699-1702 the  
5 synthesis of hydroxylamino derivatives using samarium diiodide as reducing agent.

None of the above mentioned documents mentions the use of the compounds as inhibitors of protein and/or peptide fibrils aggregation.

WO99/62505 describes a method for the treatment of a  
10 neurodegenerative disorder comprising the administration of compounds able to inhibit the binding of an amyloid beta peptide to alpha-7 nicotinic acetylcholine receptors. This patent application claims compounds of the general formula:

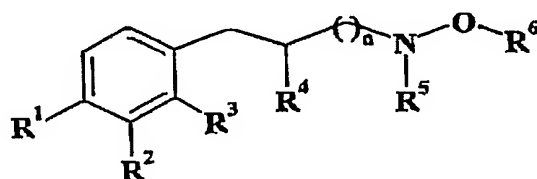


wherein R<sup>2</sup> is selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl or C<sub>7</sub>-C<sub>10</sub> aralkyl and  
15 R<sup>3</sup> is selected from hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl or C<sub>3</sub>-C<sub>10</sub> alkenyl.

WO 01/30979 discloses pharmaceutical compositions comprising primary N-hydroxylamines of the general formula NHOHCR<sub>1</sub>R<sub>2</sub>R<sub>3</sub>, wherein R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> are independently selected from hydrogen, substituted or unsubstituted (C<sub>1</sub>-C<sub>10</sub>) alkyl, alkenyl, alkynyl, aryl, acyl, carboxyl, amino,  
20 nitro, nitroso, oxime, hydrazone, azo, thiol, sulfonyl and halide and their use for reducing oxidative damage.

**DESCRIPTION OF THE INVENTION**

The present invention relates to the use of compounds of formula (I)

**(I)**

pharmaceutically acceptable salts or prodrugs thereof, wherein:

5  $n$  is 0, 1 or 2;

$R^1$  and  $R^2$ , independently of each other, are H, OH or  $OCH_3$ ;

$R^3$  is H or  $CH_3$ ;

$R^4$  is H,  $C_1$ - $C_3$  straight or branched alkyl or, together with  $R^3$ , forms a five to seven-membered carbocyclic ring;

10 and  $R^5$  and  $R^6$ , independently of each other, are H or  $C_1$ - $C_5$  straight or branched alkyl

for the preparation of pharmaceutical compositions for the prevention, treatment, diagnosis of central nervous system (CNS) disorders involving protein misfolding and/or misaggregation, for example disorders caused by  
15 formation of fibrils of beta-amyloid peptide, alpha-synuclein, prion protein and huntingtin, such as Alzheimer's Disease, systemic AA amyloidosis, Lewy body disease, Parkinson's Disease, spongiform encephalopathies and Huntington's Disease.

The invention also relates to compounds of formula (I) as defined above  
20 and pharmaceutically acceptable salts thereof with the provisos that:

$R^1$  and  $R^2$  cannot be both hydrogen;

when  $n$  is 0,  $R^1$  and  $R^2$  are both hydroxyl,  $R^3$  and  $R^5$  are hydrogen,  $R^4$  cannot be  $CH_3$  (GB 1,062,299);

when  $n$  is 0,  $R^3$  is H and  $R^4$  is H or  $CH_3$ ,  $R^6$  cannot be  $C_1$ - $C_3$  straight or

branched alkyl (U.S. 3,184,510);

and that the compounds cannot be:

1-(4-hydroxyphenyl)-2-hydroxylaminoethane, (J. Biol. Chem. 1979, 254, 8575-8583)

5 1-(4-hydroxyphenyl)-2-hydroxylaminopropane, (J. Pharm. Pharmac. 1973, 25, 708-717)

1-(4-methoxyphenyl)-2-hydroxylaminopropane, (J. Med. Chem. 1965, 8, 100-104, J. Pharm. Pharmac. 1973, 25, 708-717)

10 1-(3,4-dimethoxyphenyl)-2-hydroxylaminopropane, (J. Med. Chem. 1965, 8, 100-104, Tetrahedron 1975, 31, 1531-1535).

1-(4-methoxyphenyl)-4-hydroxylaminobutane, (Tetrahedron Letters 1991, 32, 1699-1702)

Preferred novel compounds are:

N-(5-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-hydroxylamine;

15 N-(5-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine;

N-(5-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-hydroxylamine;

N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-hydroxylamine;

N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine;

20 N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-hydroxylamine;

N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-hydroxylamine;

25 N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine;

N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-hydroxylamine;

- N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-butyl-O-ethyl-  
hydroxylamine;
- N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-butyl-O-propyl-  
hydroxylamine;
- 5 N-(5,6-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-  
hydroxylamine;
- N-(5,6-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-  
hydroxylamine;
- N-(5,6-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-  
10 hydroxylamine;
- N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-hydroxylamine;
- N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-N-methyl-hydroxylamine;
- N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-N-propyl-hydroxylamine;
- N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-N-methyl-hydroxylamine;
- 15 N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-N-propyl-hydroxylamine;
- N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-hydroxylamine;
- N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-N-methyl-hydroxylamine;
- N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-N-propyl-hydroxylamine;
- N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-hydroxylamine;
- 20 N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-N-methyl-hydroxylamine;
- N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-N-propyl-hydroxylamine;
- N-(5-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-  
hydroxylamine;
- N-(5-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-  
25 hydroxylamine;
- N-(5,6-dihydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-  
hydroxylamine;

N-(5,6-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-hydroxylamine;

N-(5-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

5 N-(5-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

N-(5,6-dihydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

10 N-(5,6-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-hydroxylamine;

N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-O-ethyl-hydroxylamine;

N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-N-methyl-hydroxylamine;

N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-N-propyl-hydroxylamine;

15 N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-N-propyl-O-ethyl-hydroxylamine;

N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-hydroxylamine;

N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-O-ethyl-hydroxylamine;

N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-N-methyl-hydroxylamine;

20 N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-N-propyl-hydroxylamine;

N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-N-propyl-O-ethyl-hydroxylamine.

Preferred known compounds for the use of the invention are:

N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;

25 N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine;

N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-hydroxylamine;

N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;

N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine;

N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;

N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine;

5 N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;

N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine;

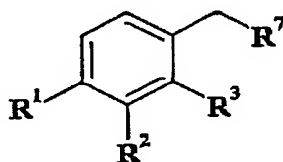
The present invention includes all the possible optical isomers of the compounds of formula (I) and their mixtures, as well as their metabolites.

10 Some crystalline forms of the compounds may exist as polymorphs, which are also included in the present invention. Some of the compounds are solvated with water, and as such they are also intended to be encompassed within the scope of the invention. The invention also includes pharmaceutically acceptable bioprecursors and prodrugs of compounds of formula (I). Selection  
15 and preparation of prodrugs are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Suitable pharmaceutically acceptable salts of compounds of formula (I) include acid addition salts with inorganic acids, e. g. nitric, hydrochloric, carbonic, hydrobromic, sulphuric and phosphoric acid, or with organic acids,  
20 e. g. acetic, propionic, glycolic, lactic, oxalic, malonic, succinic, maleic, fumaric, tartaric, citric, benzoic, cinnamic, mandelic, methanesulphonic, salicylic acid.

The compounds of the invention can be prepared by different methods.

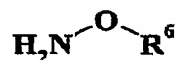
According to a first method, a compounds of formula (II)



(II)

10

wherein  $R^1$ ,  $R^2$ ,  $R^3$  are as defined above and  $R^7$  is  $-C(=O)R^4$ ,  $-\text{CH}(R^4)-\text{CHO}$ , or  $-\text{CH}(R^4)-\text{CH}_2-\text{CHO}$ , wherein  $R^4$  is as defined above is reacted with a compound of formula (III)

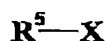


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(III)

wherein  $R^6$  is as defined above, in the presence of a reducing agent to give a compound of formula (I) wherein  $R^5$  is hydrogen. This is subsequently alkylated with a compound of formula (IV):

10



(IV)

wherein  $R^5$  is  $\text{C}_1\text{-C}_5$  straight or branched alkyl and X is a halogen atom or a leaving group, preferably selected from mesylate, tosylate or triflate.

Alternatively, compounds of formula (I) wherein  $R^5$  is hydrogen can be subjected to reductive alkylation with a compound of formula (V):

15

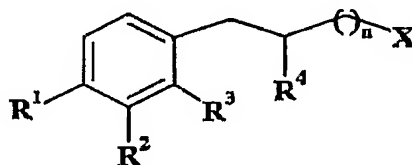


(V)

wherein  $R^8$  is hydrogen or  $\text{C}_1\text{-C}_4$  alkyl.

Compounds of formula (I) wherein  $R^5$  is hydrogen can also be obtained by reacting a compound of formula (VI)

20



(VI)

wherein  $n$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and X are as defined above with a compound of formula (VII)

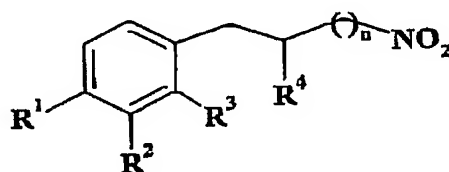
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(VII)

wherein  $R^6$  is as defined above in the presence of a base and subsequent hydrolysis of the resulting carbamate.

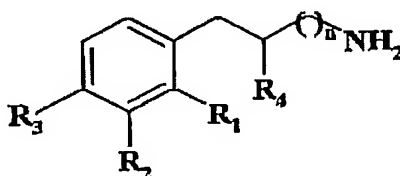
5 According to a further method, a compound of formula (VIII)



(VIII)

wherein  $n$ ,  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as defined above,  
is reduced with  $BH_3 \cdot THF$ ,  $NaBH_4$ ,  $Zn/NH_4Cl$ ,  $SmI_2$  (Kende, A.S. and Mendoza, J. S. *Tetrahedron Letters* 1991, 32, 1699-1702), to give compounds  
10 of formula (I) where both  $R_5$  and  $R_6$  are hydrogen. N- and/or O-alkylation can be performed according to methods described in the literature and well known to those skilled in the art.

The compounds of the general formula (I) wherein both  $R^5$  and  $R^6$  are hydrogen can also be obtained by alkylation of the amino group of compounds  
15 of general formula (IX)



(IX)

wherein  $n$ ,  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as defined above  
with  $YCH_2CN$  (with  $Y = Cl, Br, I$ ), oxidation with  $m$ -CPBA, and subsequent hydrolysis with hydroxylamine (H. Tokuyama *et al. Synthesis* 2000, 9,  
20 1299-1304).



Compounds (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) are commercially available or can be prepared from commercially available compounds by conventional methods.

Reductive amination is preferably performed under nitrogen atmosphere, in a suitable organic solvent, preferably an alcohol, at a temperature ranging from about 0°C to about 40°C. The reduction can be carried out with hydrides, preferably selected from NaBH<sub>4</sub>, NaBH<sub>3</sub>CN or by catalytic hydrogenation, the most appropriate catalyst being PtO<sub>2</sub>. Molecular sieves can optionally be added to the reaction mixture to promote the reaction.

10 The reaction of compounds of formula (VI) with compounds of formula (VII) is carried out in alkaline conditions, in solvents like alcohols, THF, acetonitrile, at temperatures ranging from room temperature to 100°C.

In compounds of the general formulas (IV) and (VI), X is preferably iodine or mesylate and alkylation can be carried out in a suitable organic solvent, preferably selected from methanol, ethanol or isopropanol, more preferably ethanol, at a temperature ranging from about 0°C to about 50°C.

The reductive alkylation of compounds of formula (I) wherein R<sub>5</sub> is hydrogen with an aldehyde of formula (V) can be carried out in a suitable organic solvent, such as an alcohol, e.g. methanol, ethanol or acetonitrile in the presence of a suitable reducing agent, such as sodium cyanoborohydride, at a temperature ranging from about 0°C to about 30°C.

The reduction of the nitro group of compounds of the general formula (VIII) to hydroxylamino group can be carried out according to conventional methods, preferably under nitrogen atmosphere with diborane or NaBH<sub>4</sub> in THF at a temperature ranging from about 0°C to about 25°C, or with SmI<sub>2</sub> in THF/methanol at room temperature.

The oxidation of compounds of the general formula (IX) can be carried out according to Tokuyama, H. et al. Compounds of the general formula (IX)

are first treated with  $\text{Y-CH}_2\text{CN}$ , in a suitable organic solvent, preferably acetonitrile or DMF, with a suitable base, preferably Hünig's base (N,N-diisopropylethylamine) or  $\text{K}_2\text{CO}_3$  and subsequently oxidised with m-CPBA in a suitable organic solvent, preferably  $\text{CH}_2\text{Cl}_2$ , at a temperature ranging from room temperature to  $40^\circ\text{C}$ ; the final treatment with hydroxylamine is carried out in an alcoholic solvent, preferably in boiling methanol.

### PHARMACOLOGY

The compounds of the invention are able to interfere in vitro aggregation, fibrilization and deposition of different type of self-aggregating proteins, such as  $\text{A}\beta_{1-42}$ , PrP and  $\alpha$ -synuclein.

In our experimental conditions, the peptide monomer or already aggregated was incubated at  $37^\circ\text{C}$ , alone or in the presence of the test compound, for different time intervals, then centrifuged and both the supernatant and the pellet were analyzed by HPLC or Thioflavine T binding assay.

The potencies of the compounds of this invention are in low  $\mu\text{M}$  range and at least in 1:10 molar ratio to the peptide concentration.

Pharmaceutical compositions of compounds of formula (I) for oral, parenteral, rectal, sublingual, intranasal or transdermal administration can be prepared according to conventional methods and with conventional excipients or carriers, for example as disclosed in Remington's Pharmaceutical Sciences Handbook, XVII ed., Mack Pub., N.Y., U.S.A.. The effective dose ranges from 0.1 mg/Kg and 100 mg/Kg. Optimal dosages may be determined by those skilled in the art, and will vary according to the compound, the administration route and the development of the disease. Patient-associated parameters, such as body weight, age, sex, diet, physical activity, period of administration, associated co-morbidities and clinical conditions will also be taken into account.

Preferred pharmaceutical compositions for oral administration are preferably tablets, sublingual tablets, compressed or coated pills, dragees,

sachets, hard or soft gelatine capsules. Suitable excipients or carriers include diluents, preferably lactose, dextrose, sucrose, mannitol, sorbitol, cellulose; lubricants, preferably silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binders, preferably starches, gelatine, methylcellulose, carboxymethylcellulose, arabic gum, tragacanth, polyvinylpyrrolidone; disgregants, preferably starches, alginic acid, alginates, sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, preferably lecithin, polysorbates, laurylsulphates; and, in general, non-toxic.

Liquid dispersions for oral administration are preferably syrups, emulsions, and suspensions. Suitable carriers for syrups include saccharose or saccharose in admixture with glycerine and/or mannitol and/or sorbitol. Suitable carriers for suspensions and emulsions include natural gums, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. Suitable carriers for suspensions or solutions for intramuscular injections include preferably sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol. A suitable amount of lidocaine hydrochloride can optionally be contained in injectable preparations.

Suitable carriers solutions for intravenous injection or infusion are sterile water or sterile isotonic saline.

Suitable excipients for suppositories include cocoa butter, polyethylene glycol, polyoxyethylene sorbitan fatty acid ester surfactants or lecithins.

The following examples illustrate the invention in greater detail.

#### Example 1

**N-(5,6-Dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine**

5,6-Dimethoxy-3,4-dihydro-1H-naphthalen-2-one (1.5 g, 7.5 mmol), prepared as described in *J. Med. Chem.* 1977, 20, 1111-1116, was dissolved in

water (15 ml) and a solution of O-ethylhydroxylamine hydrochloride (1 g, 10 mmol) and  $\text{Na}_2\text{CO}_3$  (0.53 g, 5 mmol) in water (10 ml) was added dropwise under stirring at 10°C. The reaction was left at room temperature overnight and then extracted with diethyl ether. The ether solution was evaporated to dryness under vacuum. The residue was dissolved in 20 ml of ethanol and concentrated hydrochloric acid (1 ml) and hydrogenated at  $3,6 \times 10^6$  Pa (50 psi) using  $\text{PtO}_2$  as catalyst. The solvent was removed under reduced pressure, water was added and the aqueous phase was treated with  $\text{NaHCO}_3$  and extracted with ethyl acetate. The organic phase was dried over  $\text{MgSO}_4$ , filtered and concentrated to dryness under vacuum. The crude residue was purified by chromatography, to afford 0.85 g of the title compound.

MS (EI): 251.0 ( $\text{M}^+$ ).

#### Example 2

**N-(5,6-Dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-hydroxylamine**

N-(5,6-Dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine (0.85 g, 3.4 mmol), obtained as described in Example 1, was dissolved in 2-pentanone (10 ml) and refluxed with 1-bromopropane (0.5 g, 4 mmol) and solid  $\text{K}_2\text{CO}_3$  (0.6 g, 4.5 mmol). The solid was filtered and the solvent was evaporated to dryness under vacuum. The crude residue (1.2 g) was purified by chromatography to afford 0.28 g of the title compound.

MS (EI): 293.2 ( $\text{M}^+$ ).

#### Example 3

**N-(5,6-Dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-hydroxylamine**

N-(5,6-Dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-hydroxylamine (0.8 g, 2.7 mmol), obtained as described in Example 2, was dissolved in 48% HBr (12 ml) and refluxed until completion of the

reaction. The solvent was evaporated to dryness under vacuum and the residue was purified by chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  90:10) to afford 0.5 g of the title compound.

MS (EI): 265.2 ( $\text{M}^+$ );

- 5  $^1\text{H}$ -NMR ( $\text{DMSO}+\text{TFA}$ )  $\delta$ : 6.62 (d, 1H); 6.41 (d, 1H); ); 4.07 (q, 2H); 3.50-3.62 (m, 1H); 3.18-3.27 (m, 2H); 2.70-3.01 (m, 3H); 2.18-2.30 (m, 1H); 1.61-1.76 (m, 3H); 1.15 (t, 3H); 0.92 (t, 3H).

The following compounds are obtained according to the same procedures described in examples 1-3:

- 10 N-(5-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-hydroxylamine;  
N-(5-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine;  
N-(5-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-hydroxylamine;  
N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-hydroxylamine;  
15 N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine;  
N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-hydroxylamine;  
N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-hydroxylamine;  
20 N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine;  
N-(5,6-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-hydroxylamine;  
N-(5-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-hydroxylamine;  
25 N-(5-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-hydroxylamine;

N-(5,6-dihydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-hydroxylamine;

N-(5,6-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-hydroxylamine;

5 N-(5-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

N-(5-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

10 N-(5,6-dihydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

N-(5,6-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine.

#### Example 4

**N-(1-Methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-O-ethyl-hydroxylamine**

15 1-(3,4-Dimethoxyphenyl)-2-propanone (1.35 g, 7.5 mmol) was dissolved in H<sub>2</sub>O (15 ml) and a solution of O-ethylhydroxylamine hydrochloride (1 g, 10 mmol) and Na<sub>2</sub>CO<sub>3</sub> (0.53 g, 5 mmol) in water (10 ml) was added dropwise under stirring at 10°C. The reaction was left at room temperature overnight and then extracted with diethyl ether. After evaporation of the solvent, the  
20 residue was dissolved in EtOH (20 ml) and concentrated hydrochloric acid (1 ml), then hydrogenated over PtO<sub>2</sub> at  $3,6 \times 10^6$  Pa (50 psi). The solvent was removed under vacuum. The residue was dissolved in 30 ml of water, the aqueous phase was made basic with NaHCO<sub>3</sub> and extracted with ethyl acetate. The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated to  
25 dryness. The crude residue was purified by flash chromatography, to afford 0.75 g of the title compound.

MS (EI): 239.3 (M<sup>+</sup>).

Example 5**N-(1-Methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine**

N-(1-Methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-O-ethyl-hydroxylamine

5 (0.3 g, 1 mmol), obtained as described in Example 4, was dissolved in acetonitrile (10 ml) and refluxed with 1-bromopropane (0.135 g, 1.1 mmol) and solid  $K_2CO_3$  (0.83 g, 6 mmol). The solid was filtered and the solvent was evaporated to dryness under vacuum. The crude residue (0.4 g) was purified by flash chromatography to afford 0.25 g of the title compound.

10 MS (EI): 281.3 ( $M^+$ ).

Example 6**N-(1-Methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine**

N-(1-Methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-N-propyl-O-ethyl-

15 hydroxylamine 0.25 g, 0.9 mmol), obtained as described in Example 5, was dissolved in 48% HBr (4 ml) and refluxed until completion of the reaction. The solvent was evaporated to dryness under vacuum and the crude residue was purified by chromatography ( $CH_2Cl_2/MeOH$  90:10) to afford 0.16 g of the title compound.

20 MS (EI): 253.3 ( $M^+$ );

$^1H$ -NMR (DMSO)  $\delta$ : 6.62 (d, 1H); 6.56 (s, 1H); 6.41 (d, 1H); 3.73 (q, 2H); 2.92-3.08 (m, 1H); 2.80-2.88 (m, 1H); 2.61-2.73 (m, 2H); 2.18-2.28 (m, 1H); 1.45-2.58 (m, 2H); 1.08 (t, 3H); 0.86-0.95 (m, 6H).

Anal. ( $C_{14}H_{23}NO_3 \cdot C_2HF_3O_2$ ) C, H, N and F.

25 The following compounds are obtained according to the same procedures described in examples 4-6:

N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-hydroxylamine;

N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;

- N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-N-methyl-hydroxylamine;  
N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-N-propyl-hydroxylamine;  
N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine;  
N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-hydroxylamine;  
5 N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;  
N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-N-methyl-hydroxylamine;  
N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-N-propyl-hydroxylamine;  
N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-hydroxylamine;  
N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;  
10 N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-N-methyl-hydroxylamine;  
N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-N-propyl-hydroxylamine;  
N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine;  
N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-hydroxylamine;  
N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-N-methyl-hydroxylamine;  
15 N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-N-propyl-hydroxylamine;  
N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-hydroxylamine;  
N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-O-ethyl-hydroxylamine;  
N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-N-methyl-hydroxylamine;  
N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-N-propyl-hydroxylamine;  
20 N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-N-propyl-O-ethyl-  
hydroxylamine;  
N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-hydroxylamine;  
N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-O-ethyl-hydroxylamine;  
N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-N-methyl-hydroxylamine;  
25 N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-N-propyl-hydroxylamine;  
N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-N-propyl-O-ethyl-  
hydroxylamine.



Example 7**Inhibition of A $\beta$  1-42 spontaneous aggregation**Preparation of the A $\beta$  1-42 peptide

Synthetic A $\beta$  1-42 (U.S. Peptide, Rancho Cucamonga, USA) was  
5 dissolved to 220  $\mu$ M in H<sub>2</sub>O/CH<sub>3</sub>CN 1:1. Aliquots of 10  $\mu$ g were lyophilized  
under vacuum with an Eppendorf concentrator for 18 h and stored at -80°C.

A $\beta$  1-42 spontaneous aggregation

10  $\mu$ g of lyophilized peptide sample was dissolved at 20  $\mu$ M in 20 mM  
potassium phosphate buffer, pH 7.4, containing 150 mM NaCl. The sample  
was incubated for 18 h at 37°C. After centrifugation at 13000xg for 5 min, the  
pellet was dissolved in formic acid and both the pellet and the supernatant  
were analysed by HPLC. The extent of aggregation was determined as the  
percentage of peptide content in the pellet compared with the total amount.

HPLC analysis of the A $\beta$  1-42 peptide monomer

15 Column: PLRP-S 100 Å, 8  $\mu$ m, 150 x 4.6 mm, Polymer Laboratories  
Mobile phase: gradient from 15% A to 70% B in 10 min  
A = H<sub>2</sub>O + 0.01% TFA  
B = CH<sub>3</sub>CN + 0.08% TFA  
Flow rate: 0.7 ml/min  
20 Detector: UV, 214 nm

Example 8**Inhibition of Non A $\beta$  Component of Alzheimer's Disease Amyloid (NAC,  
 $\alpha$ -synuclein) spontaneous aggregation**Preparation of the NAC peptide

25 The synthetic peptide NAC (Bachem) was dissolved at 1mg/ml in  
H<sub>2</sub>O/CH<sub>3</sub>CN 1:1 plus 5% TFA. Aliquots of 40  $\mu$ g were lyophilized under  
vacuum for 18 h and stored at -80°C.

NAC spontaneous aggregation

40 µg of lyophilized peptide sample was dissolved at 500 µM in 20 mM potassium phosphate buffer, pH 7.4, containing 150 mM NaCl. The sample was incubated for 24 h at 37°C. After centrifugation at 13000xg for 5 min, the pellet was dissolved in formic acid and both pellet and supernatant were analyzed by HPLC. The extent of aggregation was determined as the percentage of peptide content in the pellet compared to the total amount used.

HPLC analysis of the NAC peptide monomer

1 pump  
10 1 autosampler  
1 UV detector  
Guard column: high performance guard column, 5 µm, Vydac  
Column: Protein and Peptide C18, 5 µm, 25 x 0.46 cm, Vydac  
Mobile phase: gradient developed from 95% A to 100% B in 12 min  
15 A = H<sub>2</sub>O + 0.1% TFA  
B = CH<sub>3</sub>CN + 0.08% TFA  
Flow rate: 1 ml/min  
Detector: UV, 214 nm

Example 9**20 Inhibition of PrP 106-126 spontaneous aggregation**Preparation of the Prp 106-126 peptide

The synthetic peptide PrP 106-126 (Bachem) was dissolved at 1mg/ml in H<sub>2</sub>O/CH<sub>3</sub>CN 1:1. Aliquots of 30 µg were lyophilized under vacuum for 18 h and stored at -80°C.

**25 PrP 106-126 spontaneous aggregation**

30 µg of lyophilized peptide sample was dissolved at 500 µM in 20 mM potassium phosphate buffer, pH 7.4, containing 150 mM NaCl. The sample was incubated for 24 h at 37°C. After centrifugation at 13000xg for 5 min, the

pellet was dissolved in formic acid and both pellet and supernatant were analyzed by HPLC. The extent of aggregation was determined as the percentage of peptide content in the pellet compared to the total amount used.

HPLC analysis of the PrP 106-126 peptide monomer

- 5                           1 pump  
                          1 autosampler  
                          1 UV detector
- Guard column:   high performance guard column, 5  $\mu$ m, Vydac
- Column:           Protein and Peptide C18, 5  $\mu$ m, 25 x 0.46 cm, Vydac
- 10   Mobile phase:   gradient developed from 95% A to 70% B in 12 min  
                          A = H<sub>2</sub>O + 0.1% TFA  
                          B = CH<sub>3</sub>CN + 0.08% TFA
- Flow rate:        1 ml/min
- Detector:         UV, 214 nm

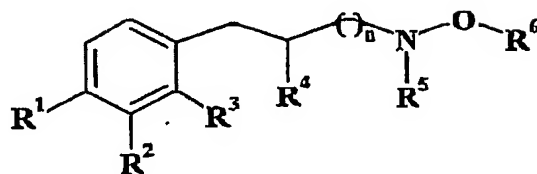
15   Example 10

**Thioflavine T (ThT) binding assay**

- After aggregation, the sample was centrifuged and the supernatant was discarded. The pellet was resuspended in 300  $\mu$ l of 50 mM glycine-NaOH buffer, pH 9.4 containing 2  $\mu$ M ThT and incubated for 5 min. The
- 20   fluorescence was determined by a fluorescence plate reader (Fusion, Packard) at a 400 nm excitation wavelength and a 485 nm emission wavelength.

**CLAIMS**

1. Use of a compound of general formula (I):



(I)

- 5 wherein:

n is 0, 1 or 2;

R<sup>1</sup> and R<sup>2</sup>, independently of each other, are H, OH or OCH<sub>3</sub>;

R<sup>3</sup> is H or CH<sub>3</sub>;

- 10 R<sup>4</sup> is H, C<sub>1</sub>-C<sub>3</sub> straight or branched alkyl or, together with R<sup>3</sup>, forms a five to seven-membered carbocyclic ring;

and R<sup>5</sup> and R<sup>6</sup>, independently of each other, are H or C<sub>1</sub>-C<sub>5</sub> straight or branched alkyl

- 15 for the preparation of pharmaceutical compositions for the prevention and treatment of central nervous system disorders involving protein misfolding or misaggregation.

2. Use according to claim 1 wherein the central nervous system disorders involve formation of fibrils of beta-amyloid peptide, alpha synuclein, prion protein and huntingtin.

3. Use according to claim 2 wherein the central nervous system diseases  
20 are Alzheimer's Disease, systemic AA amyloidosis, Lewy body disease, Parkinson's Disease, spongiform encephalopathies and Huntington's Disease and for diagnosis of said disorders.

4. The use according to any one of claims from 1 to 3, wherein the compound is selected from the group consisting of:

N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;

N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine;

N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-hydroxylamine;

N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;

5 N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine;

N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;

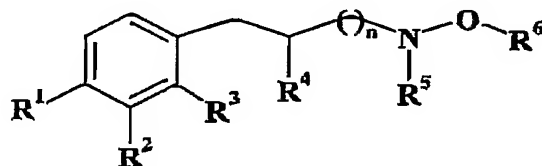
N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine;

N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-O-ethyl-hydroxylamine;

10 N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-N-propyl-O-ethyl-hydroxylamine;

and the pharmaceutically acceptable salts thereof.

5. A compound of general formula (I)



(I)

15 and pharmaceutically acceptable salts or prodrugs thereof, wherein:

n is 0, 1 or 2;

R<sup>1</sup> and R<sup>2</sup>, independently of each other, are H, OH or OCH<sub>3</sub>;

R<sup>3</sup> is H or CH<sub>3</sub>;

R<sup>4</sup> is H, C<sub>1</sub>-C<sub>3</sub> straight or branched alkyl or, together with R<sup>3</sup>, forms a five to seven-membered carbocyclic ring;

20 and R<sup>5</sup> and R<sup>6</sup>, independently of each other, are H or C<sub>1</sub>-C<sub>5</sub> straight or branched alkyl with the provisos that:

R<sup>1</sup> and R<sup>2</sup> cannot be both hydrogen;

when n is 0, R<sup>1</sup> and R<sup>2</sup> are both hydroxyl, R<sup>3</sup> and R<sup>5</sup> are hydrogen, R<sup>4</sup>

cannot be  $\text{CH}_3$ ;

when  $n$  is 0,  $\text{R}^3$  is H and  $\text{R}^4$  is H or  $\text{CH}_3$ ,  $\text{R}^6$  cannot be  $\text{C}_1$ - $\text{C}_3$  straight or branched alkyl;

and that the compounds cannot be:

- 5            1-(4-hydroxyphenyl)-2-hydroxylaminoethane,  
             1-(4-hydroxyphenyl)-2-hydroxylaminopropane,  
             1-(4-methoxyphenyl)-2-hydroxylaminopropane,  
             1-(3,4-dimethoxyphenyl)-2-hydroxylaminopropane,  
             1-(4-methoxyphenyl)-4-hydroxylaminobutane.

- 10    6.    A compound according to claim 5 selected from the group consisting of:

N-(5-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-hydroxylamine;

N-(5-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine;

- 15            N-(5-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-  
             hydroxylamine;

N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-hydroxylamine;

N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine;

N-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-  
             hydroxylamine;

- 20            N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-  
             hydroxylamine;

N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-  
             hydroxylamine;

N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-  
25            hydroxylamine;

N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-butyl-O-ethyl-  
             hydroxylamine;

- N-(5,6-dihydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-butyl-O-propyl-hydroxylamine;
- N-(5,6-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-methyl-hydroxylamine;
- 5 N-(5,6-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-O-ethyl-hydroxylamine;
- N-(5,6-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-N-propyl-O-ethyl-hydroxylamine;
- N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-hydroxylamine;
- 10 N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-N-methyl-hydroxylamine;
- N-(1-methyl-2-(3-hydroxy-phenyl)-ethyl)-N-propyl-hydroxylamine;
- N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-N-methyl-hydroxylamine;
- N-(1-methyl-2-(3,4-dihydroxy-phenyl)-ethyl)-N-propyl-hydroxylamine;
- N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-hydroxylamine;
- 15 N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-N-methyl-hydroxylamine;
- N-(1-methyl-2-(3-methoxy-phenyl)-ethyl)-N-propyl-hydroxylamine;
- N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-hydroxylamine;
- N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-N-methyl-hydroxylamine;
- N-(1-methyl-2-(3,4-dimethoxy-phenyl)-ethyl)-N-propyl-hydroxylamine;
- 20 N-(5-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-hydroxylamine;
- N-(5-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-hydroxylamine;
- N-(5,6-dihydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-hydroxylamine;
- 25 N-(5,6-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-O-ethyl-hydroxylamine;

N-(5-hydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

N-(5-methoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

5 N-(5,6-dihydroxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

N-(5,6-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl-methyl)-N-propyl-O-ethyl-hydroxylamine;

N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-hydroxylamine;

10 N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-O-ethyl-hydroxylamine;

N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-N-methyl-hydroxylamine;

N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-N-propyl-hydroxylamine;

N-(2-methyl-3-(3,4-dihydroxy-phenyl)-propyl)-N-propyl-O-ethyl-hydroxylamine;

15 N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-hydroxylamine;

N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-O-ethyl-hydroxylamine;

N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-N-methyl-hydroxylamine;

N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-N-propyl-hydroxylamine;

N-(2-methyl-3-(3,4-dimethoxy-phenyl)-propyl)-N-propyl-O-ethyl-

20 hydroxylamine.

and the pharmaceutically acceptable salts thereof.

7. Pharmaceutical compositions containing one or more compounds of formula (I) as defined in claim 1 or 5 in a mixture with suitable excipients and/or carriers.

25 8. Pharmaceutical compositions containing one or more compounds of formula (I) as defined in claim 1 and a compound for the treatment of central nervous system (CNS) disorders involving protein misfolding and/or misaggregation, for example disorders caused by formation of fibrils of beta-



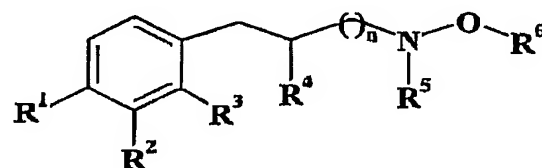
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amyloid peptide, alpha-synuclein, prion protein and huntingtin, such as Alzheimer's Disease, systemic AA amyloidosis, Lewy body disease, Parkinson's Disease, spongiform encephalopathies and Huntington's Disease, in admixture with suitable excipients and/or carriers.

5

**ABSTRACT****HYDROXYLAMINE DERIVATIVES**

5           This invention is related to hydroxylamino derivatives of the following general formula (I)



(I)

wherein

n is 0, 1 or 2;

10           R<sup>1</sup> and R<sup>2</sup>, independently of each other, are H, OH or OCH<sub>3</sub>;

R<sup>3</sup> is H or CH<sub>3</sub>;

R<sup>4</sup> is H, C<sub>1</sub>-C<sub>3</sub> straight or branched alkyl or, together with R<sup>3</sup>, forms a five to seven-membered carbocyclic ring;

15           and R<sup>5</sup> and R<sup>6</sup>, independently of each other, are H or C<sub>1</sub>-C<sub>5</sub> straight or branched alkyl

and the pharmaceutically acceptable salts or prodrug thereof, for the preparation of medicaments useful for the prevention, treatment and diagnosis of CNS degenerative disorders related to protein misfolding and/or misaggregation.

20           The invention also relates to novel compounds included in formula (I), to a method for preparing said compounds and to pharmaceutical compositions containing them.

